PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1242707-EJH	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/AU2004/000374	International filing date *(day/month/year)* 26 March 2004	Priority date *(day/month/year)* 26 March 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] A61K 31/41, 31/4164, 31/4178; A61K 31/4196, 31/4245; A61P 11/06; C07D 231/12, 233/54, 249/12, 263/32, 307/42, 317/22, 333/16, 333/18, 403/10, 403/12, 405/10, 413/10; C07K 14/47; G01N 33/50, 33/53

Applicant

CRC FOR ASTHMA LIMITED et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[ ]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
10 September 2004	9 June 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **DAVID GRIFFITHS** Telephone No. (02) 6283 2628.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000374

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1 (b))

   ☐ publication of the international application (under Rule 12.4)

   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

   ☐ the international application as originally filed/furnished

   ☒ the description:

   pages **1 - 83** as originally filed/furnished
   pages* received by this Authority on with the letter of
   pages* received by this Authority on with the letter of

   ☒ the claims:

   pages as originally filed/furnished
   pages* as amended (together with any statement) under Article 19
   pages* **84 - 90** received by this Authority on **2 June 2005** with the letter of **2 June 2005**
   pages* received by this Authority on with the letter of

   ☐ the drawings:

   pages as originally filed/furnished
   pages* received by this Authority on with the letter of
   pages* received by this Authority on with the letter of

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing (*specify*):
   ☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing (*specify*):
   ☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1 - 17	YES
	Claims	NO
Inventive step (IS)	Claims 1 - 17	YES
	Claims	NO
Industrial applicability (IA)	Claims 1 - 17	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

The present application relates therapeutic agents for treating inflammation of cells normal mammalian bronchial epithelial cells wherein the therapeutic agent reduces the levels or activity of FABP-4 (aP2) or FABP-5 (mal1).

The following citations are considered in this report:

D1. US 2003/0036070
D2. EP 1 234 878
D3. WO 2000/029621
D4. WO 2000/059506
D5. WO 2002/062848
D6. EMBL Accession ID. HSALBP and PubMed Abstract 2481498
D7. EMBL Accession ID. HSFABPHA and PubMed Abstract 1512466

US 2003/0036070 relates to methods for identifying and/or classifying patients with inflammatory bowel diseases (IBD) based on the findings that certain genes are differentially expressed in intestinal tissue of IBD patients compared with related normal cells. The citation discloses FABP-4 as one of these genes, see table 1 at page 27. The citation does not disclose or suggest the use of these genes or their products for the treatment of inflammation of bronchial cells, such as asthma, and so the present claims must be regarded as being novel and inventive.

EP 1 234 878 discloses the use of an antisense nucleotide to a disease-associated gene, which is useful as a diagnostic marker for bronchial asthma, chronic obstructive pulmonary disease, etc., an antibody against a disease-associated gene product, a method of screening a drug by using the disease-associated gene product, etc. The citation does not disclose or suggest the invention defined in the present claims.

WO 2000/029621 teaches a method for simultaneously determining the levels of selected target polynucleotide sequences and for discovering new polynucleotides and polynucleotides of diagnostic and therapeutic value; it also provides polynucleotides that have been discovered to be significantly up-regulated in tissues and body fluids of asthma patients. The citation does not disclose or suggest the invention defined in the present claims

WO 2000/059506 discloses aP2-inhibiting heterocyclic-containing biphenyl compounds defined in present formula (I) in claim 8. The citation teaches the use of these compounds for treating diabetes and other chronic inflammatory and autoimmune/inflammatory diseases; it does not teach their use for treating asthma. The citation does not teach or suggest the use of the compounds for treating inflammation of bronchial cells or as an inhalant composition and so the present claims must be acknowledged as novel and inventive over this citation.

Continued on supplemental sheet...

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [ ] in written format

   [X] in computer readable form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [ ] filed together with the international application in computer readable form

   [ ] furnished subsequently to this Authority for the purposes of search and/or examination

   [ ] received by this Authority as an amendment* on

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of Box V.

WO 2002/062848 discloses a method of regulating CCR3, which is expressed in cells involved in inflammatory expression, and is a potential target for treatment or prevention of allergic diseases including asthma. The citation does not disclose or suggest the invention defined in the present claims.

PubMed Abstract 2481498 discloses human adipocyte lipid-binding protein, which from EMBL Accession Id. HSALBP has 100% identity with present SEQ. ID. NO. 8 (aP2). The citation does not disclose or suggest therapeutic agents that reduce the levels or activity of FABP-4 (aP2) or FABP-5 (mall. The present claims must therefore be acknowledged as novel and inventive over the citation.

PubMed Abstract 1512466 discloses that PA-FABP, psoriasin, calgranulins A and B, and a few other proteins are strongly up-regulated and highly expressed in psoriatic skin. The sequence shown in EMBL Accession ID. HSFABPHA has 100% identity with present SEQ. ID. NO. 9 (FABP-5). The abstract teaches that PA-FABP mRNA is highly up-regulated in psoriatic keratinocytes but does not teach or suggest the use of compounds for treating inflammation of bronchial cells. The present claims must therefore be acknowledged as being novel and inventive.

All claims meet the criterion of being industrially applicable.

CLAIMS

1. A method for the treatment or prophylaxis of treating inflammation of normal mammalian bronchial epithelial cells said method comprising administering to a subject in need of treatment or prophylaxis a therapeutic agent which reduces the levels or activity of FABP-4 (aP2) and/or FABP-5 (mal1).

2. The method of Claim 1 wherein the mammalian bronchial epithelial cells are human bronchial epithelial cells.

3. The method of Claim 1 or 2 wherein the agent reduces the levels or activity of FABP-4 (aP2).

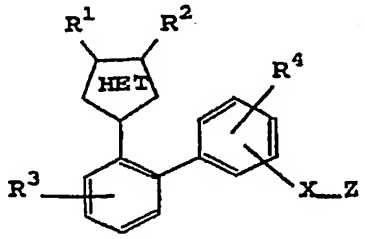
4. The method of Claim 1 or 2 wherein the agent reduces the levels or activity of FABP-5 (mal1).

5. The method of Claim 1 wherein the therapeutic agent is administered as an inhalant.

6. The method of Claim 1 wherein the subject is a human.

7. The method of Claim 1 for the treatment of asthma.

8. The method of Claim 1 or 6 or 7 wherein the therapeutic agent is a heterocyclic containing biphenyl compound of Formula I:-

I 

where:

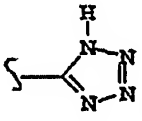
R^1 and R^2 are the same or different and are independently selected from H, alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroarylalkyl, aralkyl, cycloheteroalkyl and cycloheteroalkylalkyl;

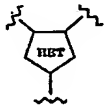
R^3 is selected from hydrogen, halogen, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, alkylcarbonyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkenylalkyl, haloalkyl, polyhaloalkyl, cyano, nitro, hydroxy, amino, alkanoyl, alkylthio, alkylsulfonyl, alkoxycarbonyl, alkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylaminosulfonyl, alkylamino, dialkylamino, all optionally substituted through available carbon atoms with l, 2, 3, 4 or S groups selected from hydrogen, halo, alkyl, polyhaloalkyl, alkoxy, haloalkoxy, polyhaloalkoxy, alkoxycarbonyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, alkylcarbonyl, acyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonyl, aminosulfinyl, aminosulfinyl, alkylsulfinyl, sulfonamido or sulfonyl;

R^4 is selected from hydrogen, halogen, alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkynyl, alkylcarbonyl, arylcarbonyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkynyl, polycycloalkynylalkyl, haloalkyl, polyhaloalkyl, cyano, nitro, hydroxy, amino, alkanoyl, aroyl, alkylthio, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylaminosulfonyl, arylaminosulfonyl, alkylamino, dialkylamino, all optionally substituted through available carbon atoms with 1, 2, 3, 4 or S groups selected from hydrogen, halo, alkyl, haloalkyl, polyhaloalkyl, alkoxy, haloalkoxy, polyhaloalkoxy, alkoxycarbonyl, alkenyl, alkynyl,

cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, acyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, aminosulfinyl, aminosulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfonyl, sulfonamido or sulfonyl;

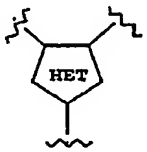
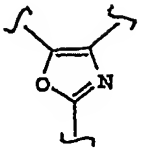
X is a bond or a linker group selected from $(CH_2)_n$, O $(CH_2)_n$, S $(CH_2)_n$, NHCO, CH=CH, cycloalkylene or N(R^5) $(CH_2)_n$, (where n = 0-5 and R^5 is H, alkyl, or alkanoyl);

Z is CO_2H or tetrazole of the formula  or its tautomer; and

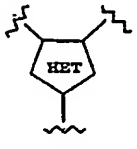
the group  represents a heterocyclic group (including heteroaryl and cycloheteroalkyl groups) preferably containing 5-members within the ring and containing preferably 1-3 heteroatoms within the ring, and which may further optionally include one or two substituents which are alkyl, alkenyl, hydroxyalkyl, keto, carboxyalkyl, carboxy, cycloalkyl, alkoxy, formyl, alkanoyl, alkoxyalkyl or alkoxycarboxyl;

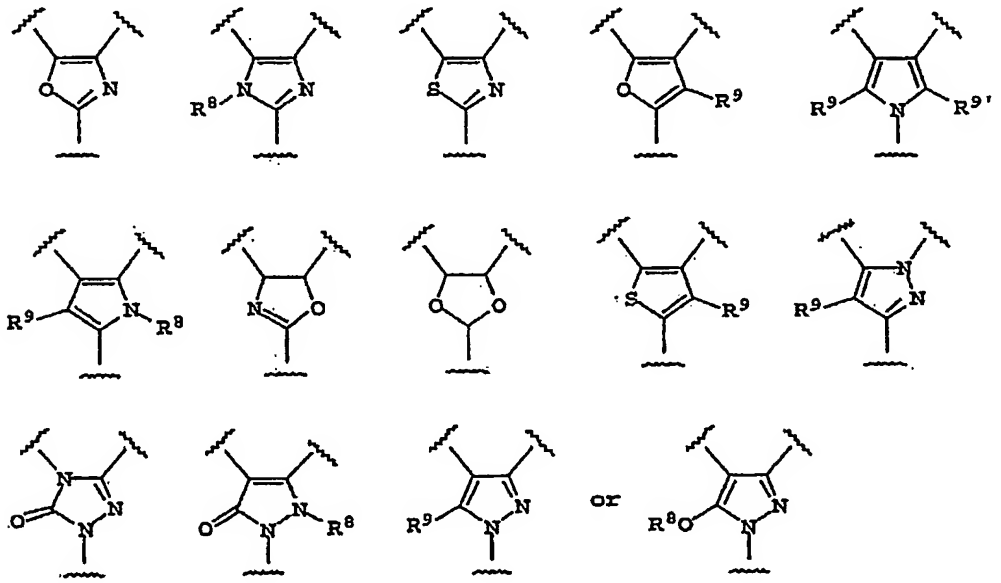
with the provisos that:

(1) n≠o when Z is CO_2H and X is O$(CH_2)_n$, S$(CH_2)_n$ or N(R^5) $(CH_2)_n$); and

(2) when  is  , then X-Z may not be O-lower alkylene-CO_2H or -O-lower alkylene-CO_2alkyl when R^1 and R^2 are both aryl or substituted aryl and R^3 and R^4 are each hydrogen;

or a stereoisomers of said compound.

9. The method of Claim 8 wherein the group  comprises a heteroaryl group and a cycloheteroalkyl group comprising:-



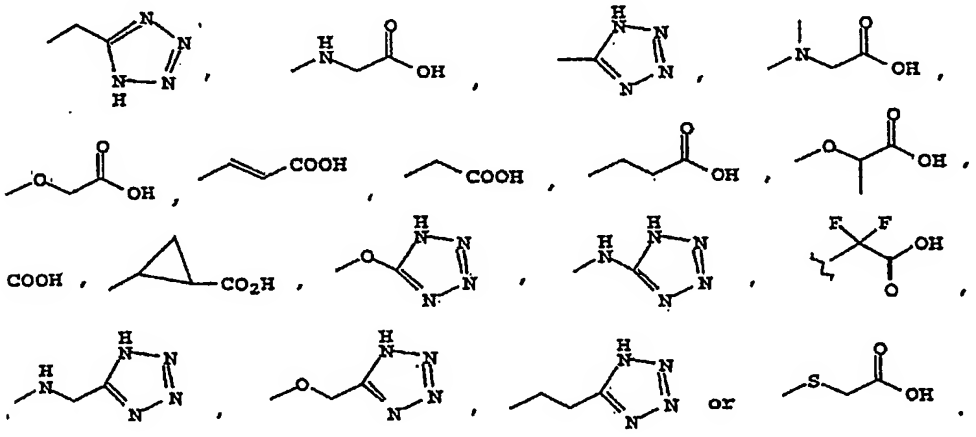
where:

R^8 is selected from H, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, or alkenyl, and

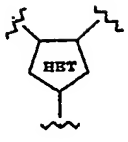
R^9 and $R^{9'}$ are the same or different and are selected independently from H, alkyl, alkoxy, alkenyl, formyl, CO_2H, CO_2 (lower alkyl), hydroxyalkyl, alkoxyalkyl, CO(alkyl), carboxylalkyl, haloalkyl, alkenyl or cycloalkyl.

10. The method of Claim 8 or 9 wherein R^8, R^9 and $R^{9'}$ groups, alkyl by itself or as part of another group comprising 1 to 6 carbons.

11. The method of Claim 8 or 9 or 10 wherein X-Z moieties comprise:-



12. The method of Claim 8 or 9 or 10 or 11 wherein:-



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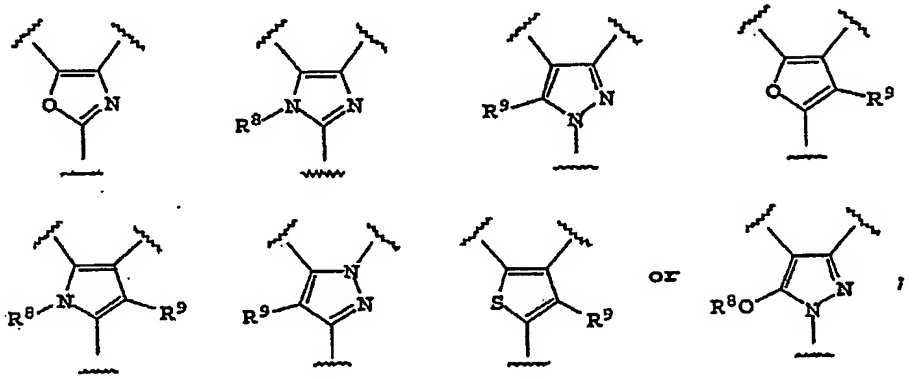


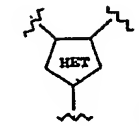
R^8 is hydrogen, alkyl, fluoroalkyl or alkoxyalkyl, and where R^9 is hydrogen, alkyl, fluoroalkyl, alkoxy or hydroxyalkyl;

R^1 and R^2 are each phenyl, substituted phenyl or cycloalkyl;

R^3 and R^4 are the same or different are independently selected from H, halo, alkyl or alkoxy; X is OCH_2, $NHCH_2$, CH_2 or CH_2CH_2; and

Z is CO_2H or tetrazole.

13. The method of any one of Claims 8 to 12 wherein:-



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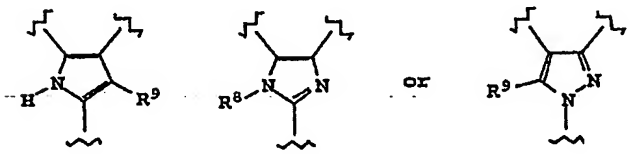

wherein:

R^8 is hydrogen, alkyl or fluoroalkyl);

R^9 is hydrogen, alkyl, fluoroalkyl or alkoxy;

R^1 and R^2 are each phenyl;

R^3 and R^4 are each H; X is OCH_2, CH_2 or $NHCH_2$; and

Z is CO_2H or tetrazole.

14. Use of a compound which reduces the levels or activity of FABP-4 and/or FABP-5 in the manufacture of a medicament for the treatment of inflammation of normal bronchial epithelial cells.

15. Use of Claim 14 wherein the inflammatory condition is asthma.

16. A method for the diagnosis of inflammation of normal bronchial epithelial cells, a propensity for development of such inflammation or for monitoring the efficacy of a therapeutic protocol to treat said inflammation, said method comprising determining the pattern of expression of FABP-4 or FABP-5 wherein up-regulated levels of FABP-4 or FABP-5 or the proteins encoded thereby is indicative of said inflammation.

17. The method of Claim 16 wherein the inflammatory condition is asthma.